IN THE UNITED STATES PATENT AND

TRADEMARK OFFICE

In reapplication of	:
Ryoichi NAGATA	:
Serial No. 10/019,396	: Group Art Unit 1615
Filed December 28, 2001	: Examiner Thurman K. Page
For: PREPARATION FOR NASAL ABSORPTION OF INSULIN	

DECLARATION UNDER 37 C.F.R. § 1.132

Honorable Commissioner of Patents
and Trademarks
Washington, D.C.

Sir:

I, Shunji Haruta, a Japanese citizen, residing at 815-5 Yoshino-cho, Kagosima 0892-0871, Japan, declare as follows:

1. I was born on the 30th of March in 1973. I completed the doctoral course in pharmaceutical sciences at Okayama University. After working as a research specialist and a hospital pharmacist in Miyazaki Medical College Hospital, I joined Translational Research, Ltd., R&D Division, in 2001.

2. To establish the differences between the claimed formulation for the nasal absorption of insulin (hereinafter "Insulin/PS-$CaCO_3$"), and that

disclosed in U.S. Patent No. 6,197,328 (hereinafter "Yanagawa (US' 328)"), the attached referential materials were prepared under my direction and supervision, and my opinions are provided below.

3. An attached Referential Material-1 includes Table-1 which listed each mean particle size and each specific surface area of 41 products of calcium carbonate offered commercially in Japan, and Figure-1 which displays the particle size range and the specific surface area range of calcium carbonate claimed by Yanagawa (US' 328) and calcium carbonate (hereinafter PS-$CaCO_3$) claimed by the applicant of the present invention together with the relationship between those listed in Table-1.

As is obvious from the distribution of references shown as the open circle symbol in Figure-1, the specific surface area increases non-linearly with decreasing the mean particle size. The distribution of calcium carbonate claimed by Yanagawa (US' 328) is observed to show the same tendency of that of references listed in Table-1. The distribution of PS-$CaCO_3$ claimed by the applicant, however, is apparent to be completely different from that of references listed in Table-1, resulting from the increased specific surface area in relation to the mean particle size of PS-$CaCO_3$, The fact strongly provides evidence that calcium carbonate claimed by the applicant is remarkably different from that claimed by Yanagawa (US' 328).

4. The assignee of the present invention conducted a clinical study of Insulin/PS-$CaCO_3$ in accordance with GCP regulation in May 2000. An attached Referential Material-2 includes Table-2 which shows serum insulin concentrations after intranasal administration of Insulin/PS-$CaCO_3$, prepared

using PS-$CaCO_3$ carrier with the particle size range of 20 – 32 μm, in 6 healthy male volunteers, and Figure-2 which displays serum insulin concentration-time profiles of Test Example 2 described in Yanagawa (US' 328) as well as that of clinical study described in Table-2.

These results indicate that serum insulin concentrations of 50 IU/50 mg $CaCO_3$/5 mg HPC-H formulation conducted as Test Example 2 in Yanagawa (US' 328), is significantly lower than those of 48 IU/48 mg PS-$CaCO_3$ conducted by the applicant, despite the addition of HPC-H as an absorption accelerator to $CaCO_3$ carrier. It should be appreciated that serum insulin concentrations of 100 IU/50 mg $CaCO_3$ formulation (without HPC-H as an absorption accelerator) conducted as Test Example 2 in Yanagawa (US' 328), is enormously lower than those of 48 IU/48 mg PS-$CaCO_3$ formulation conducted by applicant, despite the twice in insulin dose of Yanagawa (US' 328). In other words, 48 IU/48 mg PS-$CaCO_3$ formulation based on the present invention enables a higher maximum insulin concentration (approximately 1.5 folds) without HPC-H as an absorption accelerator when compared with 50 IU/50 mg $CaCO_3$/5 mg HPC-H formulation conducted in Yanagawa (US' 328), and enables a much higher maximum insulin concentration (approximately 4 - 8 folds despite the twice in insulin dose of Yanagawa (US' 328)) when compared with 100 IU/50 mg $CaCO_3$ formulation without HPC-H, prepared using $CaCO_3$ with the particle size of 20 – 45 μm and the specific surface area of 0.1 – 0.4 m^2/g.

Considering the approximate particle size range between PS-$CaCO_3$ (20 - 32 μm) conducted by the applicant and $CaCO_3$ (20 - 45 μm) conducted as Test Example 2 in Yanagawa (US' 328), it is suggested that the difference of

insulin absorbability between the two is considered to result from the difference of specific surface area between the two.

5. EPO 0,681,833A2 (hereinafter "Yanagawa (EPO' 833A)") contains the following description on page 3, lines 2-5;

"In other words, it has been found by the present inventor that the technique of homogeneously dispersing a physiologically active peptide such as calcitonin and insulin, or other physiologically active substance in a unique carrier and adsorbing said peptide or substance on the carrier provides an equal or higher bioavailability compared with that obtained by injection or oral administration." (emphasis added)

As shown in Table 1 on page 7 in Yanagawa (EPO' 833A), however, the reduced blood glucose levels after intranasal insulin administration even using hydroxyapatite, described "Hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$) as a preferable carrier in the present invention." on page 7, line 54, are inferior to those after subcutaneous insulin administration despite the 2.5 folds in insulin dose of intranasal administration. Accordingly, there is no concrete example for supporting the description on page 3, lines 2 – 5, in Yanagawa (EPO' 833A).

It should be considered that both Yanagawa (EPO' 833A) and Yanagawa (US' 328) were applied by the same inventor, and while the convention priority date of the former is May 11, 1994, the filling date of the latter is August 20, 1999. Yanagawa (US' 328) is the invention applied long after Yanagawa (EPO' 833A). It is assumed that the inventor, Yanagawa, provided to add HPC-H as an absorption accelerator to $CaCO_3$ carrier in Yanagawa (US' 328) because bioavailabilities after intranasal administration of physiologically

active peptide using $CaCO_3$ carrier described in Yanagawa (EPO' 833A) were not satisfactory.

The present invention enabling higher insulin bioavailability without such an absorption accelerator in Yanagawa (US' 328) is independent of Yanagawa (EPO' 833A) and Yanagawa (US' 328), and is an innovative technology.

6. I, the undersigned, declares further that all statements made herein of my own knowledge are true and that all statements on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonments, or both, under section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

This 27th of April, 2004.

Shujiro Yamada

Referential Material-1

The mean particle size and the specific surface area of 41 products of calcium carbonate produced commercially by 6 Japanese companies were investigated.

Table-1 Relationship between the mean particle size and the specific surface area of calcium carbonate products

Mean particle size (μm)	Specific surface area (m^2/g)	Brand name	Selling agency
0.04	25.50	CALSERIES PLS2301	Konoshima Chemical Co., Ltd.
0.09	15.00	CALSERIES PL10	Konoshima Chemical Co., Ltd.
0.10	12.00	CALSERIES PL, CALSERIES PLS505	Konoshima Chemical Co., Ltd.
0.15	8.00	CalSeries P	Konoshima Chemical Co., Ltd.
0.63	3.50	NITOREX35P	Nitto Funka Kogyo K.K.
0.74	3.00	NS#3000, NITOREX30P	Nitto Funka Kogyo K.K.
0.89	2.50	NS#2500	Nitto Funka Kogyo K.K.
0.93	2.40	NITOREX#80	Nitto Funka Kogyo K.K.
0.96	2.30	#2300	Sankyo Seifun K.K.
0.97	2.30	NS#2300, NITOREX23P	Nitto Funka Kogyo K.K.
1.03	2.15	NITOREX#75	Nitto Funka Kogyo K.K.
1.11	2.00	#2000	Sankyo Seifun K.K.
1.14	1.95	NITOREX#70	Nitto Funka Kogyo K.K.
1.17	1.90	NS#1000	Nitto Funka Kogyo K.K.
1.48	1.50	NS#600, #1500	Nitto Funka Kogyo K.K., Sankyo Seifun K.K.
1.65	1.35	P-LITE#500	Nitto Funka Kogyo K.K.
1.68	1.30	TOPFLOW H200	Ajinomoto-Fine-Techno Co., Inc.
1.71	1.30	NS#400, #800	Nitto Funka Kogyo K.K., Sankyo Seifun K.K.
1.85	1.20	NS#200	Nitto Funka Kogyo K.K.
2.02	1.10	#200	Sankyo Seifun K.K.
2.12	1.05	NS#100, MM#100	Nitto Funka Kogyo K.K.
2.22	1.00	#100	Sankyo Seifun K.K.
2.50	1.78	WHITE 18	YAKUSEN SEKKAI Co., Ltd.
2.61	0.85	SS#80	Nitto Funka Kogyo K.K.
2.70	1.65	WHITE 16	YAKUSEN SEKKAI Co., Ltd.
2.77	0.80	Super high grade	Sankyo Seifun K.K.
3.17	0.70	TS-70	Nitto Funka Kogyo K.K.
3.42	0.65	A	Sankyo Seifun K.K.
3.63	0.922	TOPFLOW H100	Ajinomoto-Fine-Techno Co., Inc.
4.44	0.50	NN#500	Nitto Funka Kogyo K.K.
4.50	1.31	WHITE 13	YAKUSEN SEKKAI Co., Ltd.

5.10	1.14	WHITE 11	YAKUSEN SEKKAI Co., Ltd.
5.56	0.40	CHINTAN 3S	Nitto Funka Kogyo K.K.
6.35	0.35	High grade	Sankyo Seifun K.K.
7.41	0.30	SS#30	Nitto Funka Kogyo K.K.
8.40	0.81	WHITE 7	YAKUSEN SEKKAI Co., Ltd.
8.89	0.25	Super high grade #3	Sankyo Seifun K.K.
9.40	0.519	TOPFLOW H50	Ajinomoto-Fine-Techno Co., Inc.
13.00	0.44	WHITE 3	YAKUSEN SEKKAI Co., Ltd.
14.80	0.15	NN#200	Nitto Funka Kogyo K.K.
59.95	0.108	Sumida B	Sumida Shokai

【Sources】

1 : Nitto Funka Kogyo K.K.
NS series : http://www.nittofunka.co.jp/HP/caco3/ca-04.html
SS・NN series : http://www.nittofunka.co.jp/HP/caco3/ca-05.html
NITOREX series : http://www.nittofunka.co.jp/HP/caco3/ca-06.html
others : http://www.nittofunka.co.jp/HP/caco3/ca-07.html

2 : Sankyo Seifun K.K.
http://www.sankyo-seifun.co.jp/product.html

3 : Konoshima Chemical Co., Ltd.
http://www.konoshima.co.jp/goods/chem/05_kstsca.htm

4 : Ajinomoto-Fine-Techno Co., Inc.
http://www.sankyo-seifun.co.jp/new-product.html

5 : YAKUSEN SEKKAI Co., Ltd.
http://www.yakusen.com/html/product/p_white.htm

6 : Sumida Shokai
Product analysis sheet

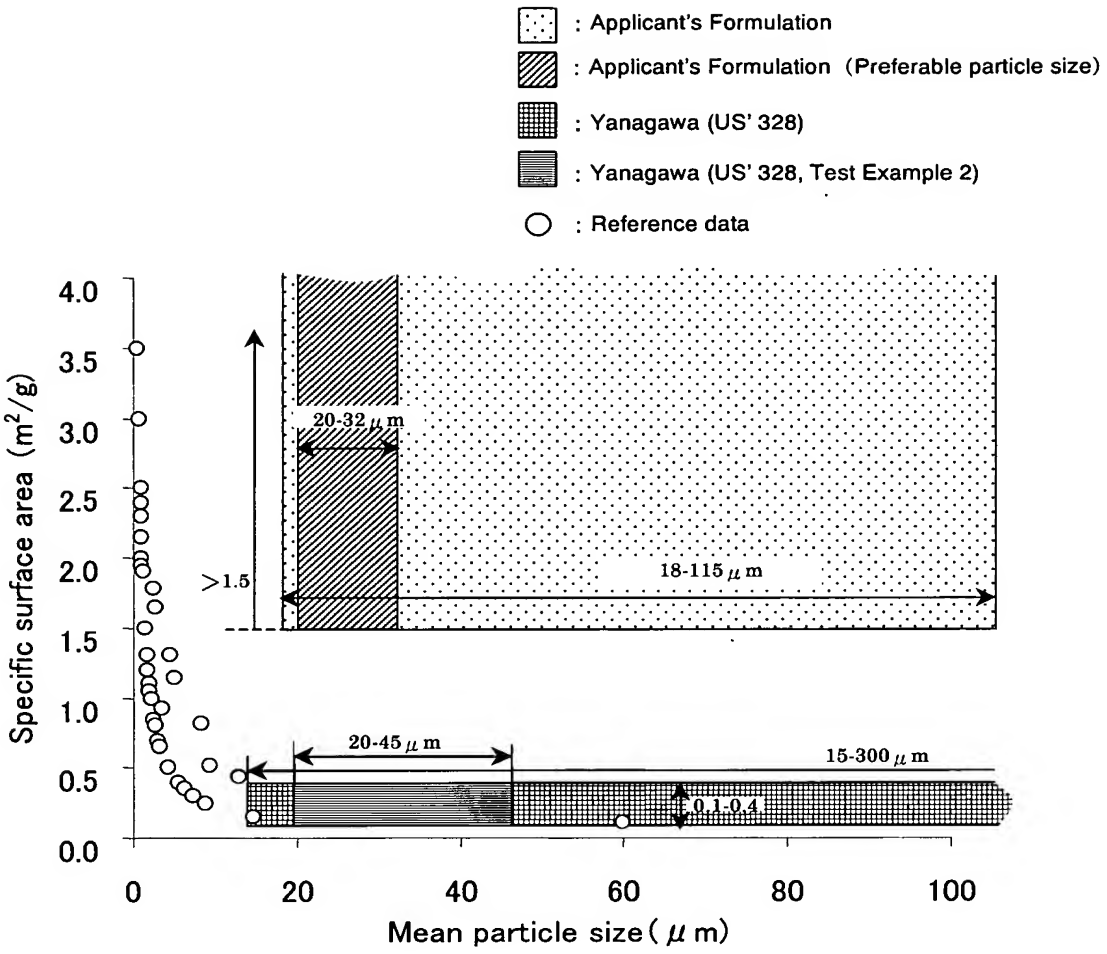

Figure-1 The particle size range and the specific surface area range of calcium carbonate claimed by Yanagawa (US' 328) and PS-$CaCO_3$ by the applicant together with those of commercially available products.

Referential Material-2

The applicant of the present invention conducted a clinical study of intranasal insulin delivery, using PS-$CaCO_3$ with the particle size range of 20 – 32 μm as a carrier, at a dose of 48 IU in 6 healthy male volunteers (22 - 42 y.o.) on May 2000. Additionally, serum insulin concentration-time profile of Insulin/ PS-$CaCO_3$ was compared to that of Test Example 2 in Yanagawa (US' 328).

Table-2 Mean serum insulin concentrations after intranasal administration of Insulin/PS-$CaCO_3$ in healthy human volunteers

Dose: 48 IU N=6	Time after administration (min)						
	0	5	10	15	30	45	60
Insulin concentration (μU/mL)	0	15.92	28.77	31.27	22.52	11.92	5.47

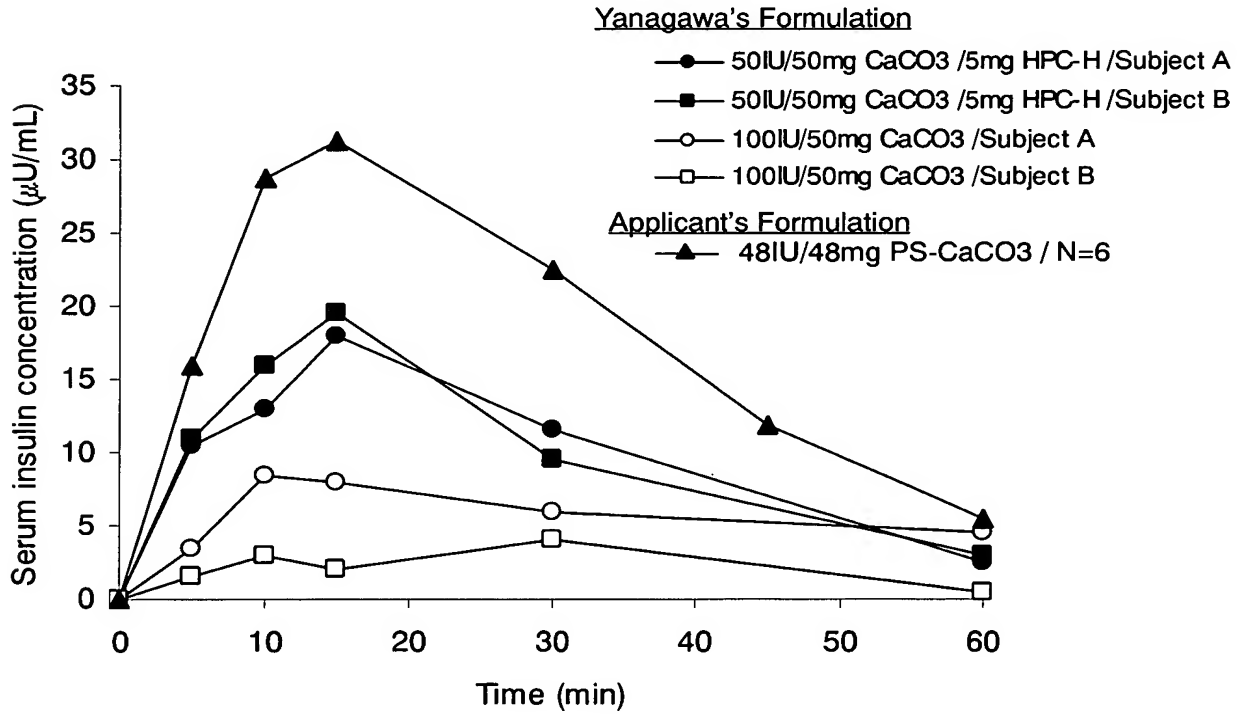

Figure-2 Comparison of serum insulin concentration profile between Yanagawa's formulati ns described in Test Example 2 of Yanagawa (US' 328) and Applicant's formulation.